Remarks

In the specification, a paragraph was added immediately after the title in order to claim benefit of the parent applications.

Claims 19-20 and 44-46 were pending in the present application. Claims 19 and 45 are amended herein. No claims were cancelled or added. Therefore, **claims 19-20 and 44-46** are pending in the application. No new matter was introduced by this amendment.

Telephone Interview

Applicants thank Examiner Ungar for the courtesy of an interview with Applicants' representative Gillian Bunker, Ph.D. on September 13, 2004. During this telephone interview, Applicants' representative inquired whether data demonstrating the efficacy of MoAbG6 for treating lung cancer *in vivo* submitted in the form of a Rule 132 Declaration would overcome the rejections under 35 U.S.C. § 112, first paragraph. Examiner Ungar pointed out that Applicants have provisionally elected group C2 (claims 19 and 20; methods of using an antibody to treat or prevent breast cancer), rather than group C5 (claims 19 and 20; methods of using an antibody to treat or prevent lung cancer). In light of the available *in vivo* data, Examiner Ungar generously agreed to consider allowing Applicants to change the election to group C5 instead of group C2. Applicants thank Examiner Ungar for considering permitting Applicants to make this change, and hereby respectfully request that they be permitted to provisionally elect group C5 (claims 19 and 20; methods of using an antibody to treat or prevent lung cancer).

Alternatively, Applicants contend that there is a nexus between breast cancer and lung cancer such that one of skill in the art, when presented with data showing that MoAbG6 reduces growth of both breast cancer and lung cancer cells *in vitro*, and that MoAbG6 reduces lung cancer growth *in vivo*, would reasonably believe that MoAbG6 would also reduce breast cancer growth *in vivo*. The majority of both breast and lung cancers are epithelial in origin (see, www.nci.nih.gov/cancertopics). The bulk of breast cancers are carcinomas, which are malignant tumors derived from epithelial tissues; less than 1% of breast cancers are sarcomas, or tumors arising from connective tissue, bone, muscle, or fat. Similarly, the bulk of lung cancers are epithelial cancers; more than 95% of lung cancers are bronchogenic carcinomas.

In addition, the majority of both breast and lung cancers are invasive. Both breast and lung carcinomas tend to invade the basement membrane, gaining access to the stroma between blood vessels, lymphatic vessels, and nerves, increasing the odds of metastasis.

Finally, many of the same chemotherapeutic agents are used to treat both breast cancer and lung cancer. These include doxorubicin, paclitaxel, docetaxel, and gemcitabine. Thus, the shared epithelial origin, propensity for metastasis, and chemotherapeutic treatments for breast and lung cancers demonstrate a nexus such that one of skill in the art, when presented with data showing the efficacy of MoAbG6 in reducing lung and breast cancer cell growth *in vitro*, and the efficacy of MoAbG6 in reducing lung cancer growth *in vivo*, would reasonably believe that MoAbG6 would also reduce breast cancer growth *in vivo*.

Declaration under § 1.132

A Declaration under § 1.132 by inventor Frank Cuttitta, Ph.D. is submitted herein. The declaration introduces data and references that demonstrate the efficacy of various inhibitors of adrenomedullin activity *in vivo*. In addition, the Declaration includes a statement from Dr. Cuttitta that the dose of MoAbG6 administered *in vivo* was equivalent to one of the *in vitro* concentrations of MoAbG6 shown to reduces growth of human lung cancer cells in the specification.

35 U.S.C. § 112, first paragraph (enablement)

Claims 19, 20, and 44-46 were rejected under 35 U.S.C. § 112, first paragraph, on the ground that the specification allegedly does not provide guidance which teaches the feasibility of *in vivo* use for an antibody to SEQ ID NO: 2 or 3 for the treatment of cancer. Applicants respectfully disagree and request reconsideration.

Applicants contend that the specification does enable *in vivo* use of an antibody to SEQ ID NO: 2 or 3 for the treatment of cancer, as discussed in the Declaration. Exhibit B of Inventor Cuttitta's Declaration under § 1.132 shows that MoAbG6 inhibits human tumor xenograft growth *in vivo*. MoAbG6 was administered to mice at a dose of 100 μg i.p. per mouse. As stated in paragraph 7 of the Declaration, this dose of MoAbG6 is equivalent to an *in vitro* concentration of approximately 5 μg/ml (100 μg per approximately 20 g mouse), which corresponds to the lowest concentration of MoAbG6 shown in Figure 16A of the present application. Therefore, as stated in the Declaration at paragraph 7, a

person of skill in the art would have known to use a dose of MoAbG6 *in vivo* (for example, about 100 μg per mouse) to achieve a tissue concentration of MoAbG6 successful in inhibiting lung cancer cell growth *in vitro*.

Furthermore, Exhibit F of the Declaration (Cuttitta *et al.*, Nature 316(6031):823-826, 1985) is a published article from a peer-reviewed journal that describes how administration of an anti-bombesin monoclonal antibody at a similar dose (200 μg per mouse i.p., three times per week) inhibits growth of human small-cell lung cancer in a mouse xenograft model (see Figure 2). As stated in the Declaration, at paragraph 6, like adrenomedullin, bombesin is a peptide hormone, and the anti-bombesin monoclonal antibody disclosed in this reference has a binding affinity for bombesin that is similar to the binding affinity of MoAbG6 for adrenomedullin (approximately 10^{-9} M). Therefore, as stated in the Declaration, paragraph 6, based on the teachings in Cuttitta *et al.* (Nature 316(6031):823-826, 1985), a person skilled in the art who knew that MoAbG6 inhibits human lung cancer cell growth *in vitro* would have expected that administration of about 200 μg MoAbG6 per mouse, three times per week, for example from about 100 to 300 μg MoAbG6 per mouse, would be successful at inhibiting adrenomedullin activity *in vivo*, and therefore would successfully inhibit human cancer growth *in vivo*, including lung cancer.

The Office action also alleges that *in vivo* use for an antibody to SEQ ID NO: 2 or 3 for the treatment of cancer is unlikely to succeed because circulating levels of adrenomedullin present in the serum would be expected to sequester the antibodies, and therefore it could not be predicted that sufficient antibody concentrations would reach the target tissue in order to effectively treat the cancer. Applicants point out that, in addition to the data presented in Exhibit B, showing that MoAbG6 inhibits human lung adenocarcinoma growth *in vivo*, (1) MoAbG6 blocks adrenomedullin function and reduces the number and size of metastases in an *in vivo* model of renal carcinoma when administered systemically to mice at a dose of 100 μg per mouse (Exhibit C), (2) intratumoral injection of another anti-human adrenomedullin antibody suppresses human glioblastoma xenograft growth *in vivo* (Exhibit D), and (3) MoAbG6 injected intraperitoneally produces significantly lower glucose responses in obese rats *in vivo* as measured by glucose tolerance test (Exhibit E). Therefore, as stated in the Declaration, paragraph 5, circulating levels of adrenomedullin present in the serum do not sequester anti-adrenomedullin antibodies sufficient to render them ineffective *in vivo*, and sufficient levels of antibody reach a variety of target tissues in concentrations sufficient to effectively treat the cancer or have other therapeutic effects, for example, lowering blood glucose. Thus, applicant respectfully requests that this rejection be withdrawn.

Claims 19 and 45 are also rejected under 35 U.S.C. § 112, first paragraph because the claims allegedly read on both treatment and prevention of cancer. Claim 19 has been amended to remove the word "prevent," and claim 45 has been amended to specify that "the method is a method of treating the subject." Applicants respectfully request that this rejection be withdrawn.

35 U.S.C. § 112, first paragraph (written description)

Claims 19, 20, and 44-46 were rejected under 35 U.S.C. § 112, first paragraph on the grounds that the claims allegedly contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. Applicants argue that original claims 1 through 4 filed with International Application Number PCT/US96/13286 on August 19, 1996, meet the written description requirement. The text of those claims is as follows:

1. A peptide selected from the group consisting of PO70 (SEQ ID NO:1), PO71 (SEQ ID NO:2), PO72 (SEQ ID NO:3), AM 94-114 (SEQ ID NO:4), AM 444-464 (SEQ ID NO:5), AM 289-309 (SEQ ID NO:6), or PAMP-20 (SEQ ID NO:7).

2. An antibody reactive with at least one peptide of claim 1.

3. A method of **preventing or treating** cancer by contacting the cancerous cells with an effective amount of the adrenomedullin peptides of claim 1 or the adrenomedullin antibodies of claim 2.

4. The method of claim 3 wherein the cancerous cells are selected from the group consisting of adrenal, nervous system, lung, colon, ovarian, or breast cancerous cells.

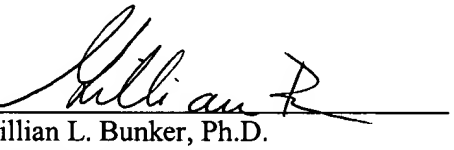
It is clear that at least as of the filing date of the PCT application, Applicants conceived of methods of using the disclosed antibodies and peptides for treating at least adrenal, nervous system, lung, colon, ovarian, or breast cancer. Therefore, Applicants respectfully disagree with the rejection and request that the rejection be withdrawn.

Conclusion

On the basis of these arguments and the amendments submitted herein, it is respectfully submitted that the present claims are in a condition for allowance. If any issues remain, the Examiner is requested to contact the undersigned attorney prior to issuance of the next Office action in order to arrange a telephone interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution and allowance of the claims.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

By 
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